REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. AMENDMENTS TO THE CLAIMS

Applicant has added new dependent claims 86-89 directed to arrays further comprising further nucleic acid molecules or probes having nucleic acid sequences consisting of a sequence selected from the group consisting of SEQ ID NOS: 1-11, 13-14, 16-20, 27-34, 36-43 and 45-47, or to arrays comprising nucleic acid molecules or probes having nucleic acid sequences consisting of SEQ ID NOS: 1-47, respectively.

Applicant respectfully requests entry of these new claims after final because, as dependent claims, if the prior art rejections of the base claims are overcome, these claims likewise will be patentable over the prior art. *See* MPEP 2143.03 ("If an independent claim is nonobvious under 35 U.S.C. § 103 then any claim depending therefrom is nonobvious."). To facilitate examination after final, Applicant agrees not to argue that new claims 86-89 are separately patentable over the prior art, although Applicant reserves the right to do so if an RCE or continuing application is filed.

Moreover, Applicant submits that these claims could not have been presented earlier because of Applicant's misunderstanding of the Restriction Requirement issued April 19, 2007. Applicant's records indicate that, prior to responding to the Restriction Requirement, Applicant's representative telephoned the Examiner to clarify the Restriction, and from that conversation understood that Applicant should limit the claims to ten sequences. It was only during the telephonic interview conducted on July 27, 2009, when Applicant first learned that the Restriction Requirement may have been misunderstood and, in the Interview Summary issued July 29, 2009, the Examiner explained that the Restriction Requirement did not actually impose "any requirement to elect only 10 sequences," but rather to elect "a specific combination" of sequences." The Interview Summary explains further that because this application is a national phase of a PCT application, "the inclusion of additional SEQ ID NO[S] into the claims may not be precluded by lack of unity practices."

Applicant believes that commercial embodiments of the claimed arrays are likely to include more than the elected combination of 10 sequences, and may very well include each of the 47 sequences set forth in SEQ ID NOS: 10-47. Thus, the new claims are of commercial significance.

For at least the foregoing reasons, Applicant respectfully urges that new claims 86-89 be entered after final.

II. SUBSTANCE OF INTERVIEWS

Applicant thanks Examiner Pohnert and Examiner Schultz for the courtesies extended during the in-person interview on June 3, 2009, and the telephone interview on July 27, 2009. Applicant's statement of the substance of the interviews is set forth below, in accordance with 37 CFR §1.113(b) and MPEP 713.04.

(a) June 3, 2009 Interview

Present at the interview were Examiner Pohnert, Patricia Folkins (Agent for the Applicant) and Robert Shipman (inventor/Applicant). There were no exhibits shown or demonstrations conducted during the interview. The merits of currently rejected claims 49-50 and 78 were discussed. In particular, the obviousness rejection of these claims in view of Denefle et al. (WO02/46458), Dean et al, Monahan et al, Schmitz (WO00/18912), GenBank AC069137.6, Boyd et al, GenBank U63970.1, Wan et al, Kruh et al, GenBank Z31010.1 and Ota et al was discussed.

The Examiner agrees that the art of record does not teach nucleic acid sequences consisting of the claimed nucleic acid sequences. The Examiner argues that the ordinary artisan would have a reasonable expectation of success obtaining additional functionally equivalent probes from the known full length sequences. The Examiner contended that absent secondary considerations, the claimed arrays are obvious as the prior art discloses nucleic acids comprising the sequences, microarrays and motivation to examine expression patterns of ABC transporters. A discussion about the requisite evidence for secondary considerations took place without any agreement.

The Applicant argued that it is irrelevant whether additional functionally equivalent DNA molecules could be obtained. They are not claiming those molecules. The question is whether or not a person skilled in the art would have a reasonable expectation of success obtaining the same molecules, or structurally similar ones, to those being claimed.

A discussion about strategies involving arguments that the presently claimed array is different from the standard (for e.g. uses sequences of different lengths) also took place.

No agreement was reached.

(b) July 27, 2009 Interview

Examiner Pohnert, Examiner Schultz, Courtenay Brinckerhoff and Michael Yamauchi (Agents for the Applicant) participated in the July 27, 2009 interview.

As discussed in more detail below, the Applicant emphasized that the claims are directed to specific probes having specific sequences that are not taught or suggested by the cited references. The Applicant questioned the applicability of the "functional equivalents" doctrine when no prior art probes had been cited to which the claim probes might be functionally equivalent. The Applicant also referred to the declaration evidence showing that the claimed probes were not functionally equivalent to those that might be derived using computer programs.

The Applicant explained that claims directed to arrays with only the 10 recited sequences would be unduly narrow, particularly where the application describes other probe sequences that would be useful if included in an array with the recited sequences. This discussion led to the discussion of the Restriction Requirement, and the previous election of 10 sequences, referenced above.

No agreement was reached.

III. RESPONSE TO FINAL OFFICE ACTION

A. The Obviousness Rejection

The final Office Action maintains the rejection of claims 49, 50 and 78 under §103(a), citing the following references: (i) Denefle *et al.* ("Denefle", WO02/46458); (ii) Dean *et al.* ("Dean", J. Lipid Res., 42:1007-1017, 2001); (iii) Monahan *et al.* ("Monahan", WO02/071928);

(iv) Schmitz (WO00/18912); (v) GenBank accession number AC069137.6 (GI:14589784); (vi) Boyd *et al.* ("Boyd", WO01/62977); (vii) GenBank accession number U63970.1 (GI:1764161); (viii) Wan *et al.* ("Wan", WO2002/74979); (ix) Kruh *et al.* ("Kruh", WO99/49735); (x) GenBank accession number Z3101.1 (GI:479155), and (xi) Ota *et al.* ("Ota", EP1074617A2). Applicant respectfully traverses.

As reflected in the pending independent claims, the present invention is directed to arrays comprising two or more nucleic acid molecules immobilized on a substrate, wherein at least two of the nucleic acid molecules have a nucleic acid sequence consisting of a sequence selected from the group consisting of SEQ ID NOS:12, 15, 21-26, 35 and 44, respectively (claim 48) or to arrays comprising a substrate having immobilized in distinct spots thereon at least 10 nucleic acid probes, wherein 10 of the probes have nucleic acid sequences consisting of SEQ ID NOS:12, 15, 21-26, 35 and 44, respectively (claim 78). Such arrays are not taught or suggested by the cited references.

At the outset, the Office Action admits that the cited references do not teach the specific probes recited in the claims, *e.g.*, probes consisting of SEQ ID NOS:12, 15, 21-26, 35 or 44. Office Action, page 6. Thus, the obviousness inquiry should end here, as the cited references admittedly do not make out a prima facie case of obviousness. *See* MPEP § 2141.03 ("All words in a claim must be considered in judging the patentability of that claim against the prior art.").

The Office Action nevertheless asserts that the claimed arrays are obvious, weaving a winding path from the teachings of the cited references to the claimed arrays that only could be maneuvered with the roadmap provided by the present application.

As taught in the specification, the recited probes are useful for uniquely identifying nucleic acid molecules that encode different human ABC transporters. Denefle is cited for teaching that the "characterization of new ABC genes will yield important transporter genes," and that its probes can be "immobilized on a support, . . . [and] ordered into matrices such as 'DNA chips.'" Office Action, page 5. Dean is cited for teaching that "the ABC transporter family comprises 48 known ATP driven transporters, which have numerous important biological functions." Office Action, page 6. The other references are cited for teaching full-length ABC

transporter gene sequences, including genomic sequences, that comprise the sequences of the recited probes. The Office Action asserts that it would have been obvious to use the prior art sequences in the array of Denefle, and that "[t]he artisan would be motivated to combine the [prior art] sequences . . . because Dean teaches ABC gene transporters are important." Office Action, page 8. According to the Office Action, "the substitution or addition of the [prior art] sequences . . . would produce a microarray with probes equivalent to the recited SEQ ID NO." Office Action, page 8. Apparently, the Examiner believes that because full-length ABC transporter gene sequences were known, one of skill in the art would have been motivated to make an array of probes useful for identifying the expression of specific genes, and such a (fictional) array would be functionally equivalent to the claimed arrays, thereby rendering the claimed arrays obvious. Applicant respectfully disagrees on several grounds.

B. The References Provide No Motivation To Make An Array As Claimed

The cited references do not provide any motivation, or reveal any reason, to make an array as claimed. As taught in the specification, the claimed arrays are useful for detecting ABC transporter gene expression, and for indentifying which specific ABC transporter genes are being expressed. The cited references do not reveal any particular interest in ABC transporter gene expression, but instead are directed to identifying ABC transporter genes *per se*, and studying the functions of the different encoded proteins.

For example, Denefle discloses ABC reporter genes, means for detecting polymorphisms and mutations therein, and the identification of specific alleles thereof. The Office Action cites Denefle's statement at page 3 that "characterization of new genes . . . is likely to yield biologically important transporters," but this teaching does not provide any motivation or reason to study the expression of known ABC transporter genes, as permitted by the claimed arrays. Moreover, Denefle's only reference to a kit comprising multiple probes teaches that the probes can comprise the full-length sequences or a "fragment or variant" thereof. This statement certainly does not provide any motivation to prepare an array of probes, each of which is capable of uniquely identifying one of the ABC transporter genes, as provided by the present invention.

Likewise, while the Abstract of Dean promises a review of "the current knowledge of the human ABC genes," Dean's actual focus is on the proteins. Thus, when Dean discusses "gene expression" it is referring to expression of proteins encoded by the genes. Dean makes no mention of gene expression *per se*, gene expression analysis, or a microarray suitable for doing so.

The Office Action fails to recognize that it is only the instant application that provides a reason to study ATP transporter gene expression *per se*. As noted at page 2 of the specification, it is only the present inventors who have recognized that studying ABC transporter gene expression in specific cells could be useful to designing and selecting specific drug treatment protocols that would be effective in the specific target cells. For example, knowing which ABC transporter genes are being expressed in target cells can be used to determine whether a particular drug might be effective for the patient at hand and/or whether a particular patient might be a suitable candidate for a specific drug therapy. The claimed arrays are useful in carrying out such studies.

Because the cited references fail to provide any reason or motivation to even make an array that would perform the same function as the claimed arrays, the obviousness rejection is improper and should be withdrawn.

C. Full-Length Sequences Do Not Render The Claimed Probes Obvious

The full-length prior art sequences do not render obvious the specific probes recited in the instant claims. In this regard, Applicant refers to several "unpublished" Board decisions on point. While these decisions are not binding, they apply legal principles that are applicable to the present case, and so provide useful guidance.

At the outset, Applicant recognizes that knowledge of a full-length sequence may render obvious an undefined "probe" for that sequence, or a probe define only by, for example, length and hybridization. *See, e.g., Ex parte Bandman*, Appeal No. 2003-1805; Application No. 09/079,892 (copy attached). The instant claims, however, are not so broad, but instead recite probes ***consisting of*** specific sequences. Under such circumstance, the specifically defined

probes are not obvious unless there is a "particular recognition or suggestion of the specific sequences" in the cited art. *Ex parte Kolberg*, Appeal No. 97-2532; Application No. 08/427,569, page 9 (copy attached).

In *Kolberg*, the Examiner had based the obviousness rejection on the published full-length sequence and general knowledge about making hybridization probes. *Kolberg*, pages 6-7. Similar to the Office Action here, the Examiner's Answer had "[s]imply opin[ed] that 'any oligonucleotide probe from the HTLV-1 sequences of [the prior art] are deemed functionally equivalent to the claimed oligonucleotides' . . . without a factual basis." *Kolberg*, page 9. The Board reversed the rejection, finding the record "insufficient to establish a conclusion of obviousness." *Kolberg*, page 9.

Although *Kolberg* was decided prior to *KSR*, it invokes the principles of *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988), which the Federal Circuit has cited post-*KSR* for differentiating "between proper and improper applications of 'obvious to try.'" *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). As noted in *Kolberg,* the only way for the skilled artisan to arrive at specifically defined probes when the cited art provides no suggestion of the specifically claimed sequences is to "'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.'" *Kolberg,* page 9 (citing *O'Farrell* 853 F.2d at 903). This same passage of *O'Farrell* was cited this year by the Federal Circuit in *Kubin* as describing when "***courts should not succumb to hindsight claims of obviousness***." *Kubin*, 561 F.3d at 1359 (emphasis added). *See also Proctor & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009) (applying the principles of *O'Farrell* under the rubric of *KSR* to find a specific chemical compound non-obvious).

As noted above and recognized in the Office Action, the present record reveals no particular recognition of the significance of the claimed sequences, and no suggestion to design probes based thereon. Thus, as with the claims determined to be non-obvious in *Kolberg* and

Proctor & Gamble, the only way the skilled person might have arrived at the claimed invention was by "merely throw[ing] metaphorical darts at a board filled with combinatorial prior art possibilities;" the Federal Circuit has confirmed that such circumstances do not amount to obviousness under *KSR*. *Kubin*, 561 F.3d at 1359.

D. The Claimed Probes Are Not Equivalent To Full-Length Sequences

The Office Action alleges that "it would have been . . . obvious . . . to use the sequences taught [in the prior art] in the array taught by Denefle." Office Action, page 7. However, there is no evidence that such an array would be functionally equivalent to the claimed array. As set forth in the specification and explained in Applicant's previous responses, the claimed arrays comprise probes that each uniquely identify a single ABC transporter gene out of a family of at least 47 human ABC transporter genes known at the time of filing. There is no evidence that the prior art sequences, which include full-length, genomic sequences, could perform this function. Indeed, such full-length sequences would not be suitable for use as probes on an array because of their length (thousands or tens of thousands of nucleotide bases) and likely regions of homology.

Another unpublished Board decision, *Ex parte Weichselbaum*, Appeal No. 1999-1458; Application No. 07/943,812 (copy attached), is instructive. At issue in that case was the patentability of a construct that included a radiation-responsive promoter. Constructs comprising the promoter were known, but not where the promoter was linked to a gene encoding a therapeutic peptide, as claimed. According to the Examiner, the radiation-inducibility was an inherent property of the promoter, and it would have been obvious to substitute one promoter for another. *Weichselbaum*, pages 6-7. According to the Applicant, the radiation-inducibility was an unexpected property that was not taught or suggested by the cited art. *Weichselbaum*, page 7. The Board determined that the record did not support the rejection because there was no evidence that the prior art promoters that had been linked to genes encoding therapeutic peptides were radiation-responsive. *Weichselbaum*, page 9. Thus, there was no evidence that the prior art promoters were, in fact, "equivalent." *Id.*

In the present case, there is no evidence that any array based on the known ABC transporter genes would be functionally equivalent to the claimed array, *e.g.*, would be useful for identifying specific ABC transporter gene(s) out of a family of at least 47 human ABC transporter genes known at the time of filing. Thus, the obviousness rejection is improper and should be withdrawn.

E. The Claimed Probes Cannot Be Held Obvious Over Fictional Prior Art

The present record also reveals no specific probes or arrays of probes to which the claimed arrays, which comprise specifically defined probes, might be functionally equivalent. Thus, the doctrine of "functional equivalence" cannot be applied to the pending claims. As stated in MPEP § 2144.06, "[i]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." Here, there is no recognition that the claimed arrays or probes are functionally equivalent to prior art arrays or probes. Indeed, no specific prior art arrays or probes have been identified. In essence, the invention has been rejected over hypothetical, fictional prior art that does not even exist.

In addition to being contrary to law, this rejection places Applicant in the impossible position of needing to establish that the claimed arrays of probes are not functionally equivalent to fictional probes, whose specific properties and functions cannot be ascertained, tested or compared. Indeed, MPEP § 716.02(e) expressly states that "applicant is ***not*** required to compare the claimed invention with ***subject matter that does not exist in the prior art***" (emphasis added). The MPEP cites *In re Chapman*, 357 F.2d 418 (CCPA 1966), for the proposition that "[r]equiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention . . . 'would be requiring comparison of the results of the invention with the results of the invention,'" which is exactly what Applicant was improperly asked to do here.

Applicant nevertheless attempted to address this issue in the Declaration of Dr. Shipman submitted with the previous response, where Applicant compared the claimed probes to probes that resulted from the use of known primer selection computer programs, when used to generate probes based on the ABC transporter genes corresponding to the probes recited in the claims. In performing this analysis, Applicant used information that would ***not*** have been available to the skilled artisan without knowledge of the present application, such as target PCR product sizes. Shipman Declaration, ¶ 16. Even then, the program did not identify the claimed probe sequences or even sequences that were equivalent thereto. As Dr. Shipman explained, the data obtained indicate that the claimed probes would be better at identifying their targets under stringent conditions than the comparison probes. Shipman Declaration, ¶ 17, Thus, Dr. Shipman concludes that commonly used primer design software does not generate probes that would be functionally equivalent to the recited probes. Shipman Declaration, ¶ 18.

The Office Action alleges that the Declaration is not persuasive because, allegedly, the skilled artisan would have undertaken the same steps that the present inventors took to arrive at the present invention, *e.g.*, the same verification, validation and selection steps. Office Action, page 3. This assertion is made without any support whatsoever, and again leaves Applicant tilting at windmills, because the record is simply devoid of any evidence of any motivation that would have led a skilled person to even attempt to design an array as claimed, let alone of the parameters that might have guided such an undertaking. To the contrary, Dr. Shipman attested that "the prior art does not teach the necessary information that would allow a person skilled in the art to identify probe sequences such as the specific nucleic acid sequences found in the Application." Shipman Declaration, ¶ 15. It is this uncontroverted testimony, rather than the Examiner's unsupported musings, that must be given weight when assessing obviousness. *See, e.g.*, MPEP § 2145 ("Office personnel should consider all rebuttal arguments and evidence presented by applicants.").

In light of these remarks, reconsideration and withdrawal of the obviousness rejection are respectfully requested.

CONCLUSION

Applicant believes that the application is condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned at the telephone number set forth below, or to contact Patricia Folkins at 416 364 7311.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date August 28, 2009 By Courtenay C. Brinckerhoff

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

Paper No. 36

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte OLGA BANDMAN, JENNIFER L. HILLMAN, PREETI LAL, KARL J. GUEGLER, GINA GORGONE, NEIL C. CORLEY, CHANDRA PATTERSON, and MARIAH R. BAUGHN

Appeal No. 2003-1805
Application No. 09/079,892

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and GRIMES, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 25 through 28 and 33 through 37. Claims 6 through 12 are pending and have been allowed. Claims 29 through 32 are also pending but have been withdrawn from consideration by the examiner. Claims 25 and 33 are representative of the subject matter on appeal. Since claim 25 refers to allowed claim 7, we reproduce claims 7, 25, and 33 as follows:

7. An isolated and purified polynucleotide comprising a polynucleotide sequence as shown in SEQ ID NO:4, wherein said polynucleotide of SEQ ID NO:4 encodes a polypeptide having glutamine fructose-6-phosphate amidotransferase activity.

25. A method for detecting a target polynucleotide in a sample, wherein said target polynucleotide comprises the polynucleotide of claim 7, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

33. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:4,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

The examiner relies upon the following references:

Nishi et al. (Nishi '713)	5,876,713	Mar. 2, 1999
Eur. Pat. App. (Nishi EPA)	EP 824,149 A2	Feb. 18, 1998

Claims 33 through 37 stand rejected under 35 U.S.C. § 112, first paragraph (written description). Claims 25 through 28 and 37 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness, the examiner relies upon Nishi '713 and Nishi EPA in the alternative. We reverse the written description rejection and affirm the obviousness rejection.

Background

The present invention involves human carbohydrate metabolism enzymes referred to by appellants as "CARM." Specification, page 5. As seen from claims 7, 25, and 33 reproduced above, the claims under review in this appeal involve the polynucleotide sequence as shown in SEQ ID NO:4 which is said to code for CARM-1. Id., page 19, lines 14 through 20. As explained:

> CARM-1 has chemical and structural similarity with human glutamine: fructose-6-phosphate amidotransferase (GI 183082). In particular, CARM-1 and human glutamine: fructose-6-phosphate amidotransferase share 78% identity. A fragment of SEQ ID NO:4 from about nucleotide 243 to about nucleotide 260 is useful, for example, as a hybridization probe. Northern analysis shows the expression of this sequence in various libraries, at least 51% of which are immortalized or cancerous and at least 46% of which involve immune response. Of particular note is the expression of CARM-1 in gastrointestinal, male and female reproductive, and nervous tissues.

Id., page 20, lines 4 through 11.

Discussion

1. Written description.

The examiner considers that claims 33 through 37 do not comply with the written description requirement of 35 U.S.C. § 112, first paragraph, since:

> The specification defines an 'allelic sequence' (see page 10) as an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered and that any given natural or recombinant gene may have none, one or many, allelic forms, and that common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, substitutions of nucleotides each of which may occur alone or in combination with the others one or more times in a given sequence. This definition does not provide any specific information about the structure of naturally occurring (alleles) variants of SEQ ID NO:4 (i.e. where are the regions within which mutations are likely to occur) nor discloses any function for naturally occurring variants. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:4 relates to the structure of any naturally

> occurring alleles. The general knowledge in the art concerning alleles does not provide any indication of how one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art structure of one does not provide guidance to the structure of others. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e. the sequence encoding SEQ ID NO:2) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Examiner's Answer, paragraph bridging pages 3 and 4.

The examiner also

> [F]ully acknowledges appellants' recitation of the structural limitations of the polynucleotides of claim 33 parts b) and d)-e). However, the polynucleotides as defined in claim 33 parts b) and d)-e) encompass a genus of polynucleotides that encompasses widely variant species, some having the same functions as the polypeptide of SEQ ID NO:1, some having unknown and distinctly different functions and some possibly having no function. While one of skill in the art, provided the polynucleotide sequence of SEQ ID NO:4, may be able to recognize variants of SEQ ID NO:4 with nucleotide sequence sharing 90% identity, one cannot recognize which of these variants occurs naturally and is thus encompassed by the genus of claim 33 part b). Therefore, the skilled artisan would not be able to recognize a member of the claimed genus of polynucleotides merely from its structural definition. This enormous genus will encompass a wide variety of polynucleotides with their own distinct properties. Because appellants have provided no functional limitation for the claimed polynucleotides, the single disclosed polynucleotide of SEQ NO:4 is not representative of the entire genus and one of skill in the art would not recognize that appellants were in possession of all polynucleotides comprising a naturally-occurring polynucleotide having at least 90% identity to SEQ ID NO:4 as encompassed by the claims.

Examiner's Answer, paragraph bridging pages 11 and 12.

The Federal Circuit discussed the application of the written description requirement to inventions in the field of biotechnology in University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), stating

that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials" Id. at 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

In reviewing this rejection, we note that the examiner has not rejected claim 8 under this section of the statute. Claim 8 reads:

8. An isolated and purified polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to the polynucleotide of SEQ ID NO:4, wherein said naturally occurring polynucleotide sequence encodes a polypeptide having glutamine-fructose-6-phosphate amidotransferase activity.

As seen, claim 8 differs from claim 33 b) which is the focus of the examiner's written description rejection in that it adds the limitation that the naturally occurring polynucleotide sequence encodes a polypeptide having glutamine-fructose-6-phosphate amidotransferase activity. Since the examiner has conceded that a claim having the scope of claim 8 complies with the written description requirement of 35 U.S.C. § 112, we do not find that the lack of a statement of function in claim 33 b) means that that portion of the claim lacks written descriptive support.

Claim 33 b) defines a genus of polynucleotides by way of two significant qualifiers. First, the polynucleotide of claim 33 b) must be "naturally occurring." Second, the polynucleotide of claim 33 b) must be "at least 90% identical to the polynucleotide sequence of SEQ ID NO:4." As explained in Lilly, a genus of polynucleotides can be described by a representative number of polynucleotides sharing common structural features which constitute a substantial portion of the genus. The examiner is correct in his analysis that claim 33 b) includes so-called nonfunctional alleles. However, those nonfunctional alleles must be "naturally occurring" and be at least "90% identical to the polynucleotide sequence of SEQ ID NO:4." In our view, these two limitations adequately describe the genus of polynucleotides encompassed by claim 33 b) without that claim further including a functional limitation.

We understand the examiner's concern that one may not recognize that a polynucleotide sequence having 90% identity with that of SEQ ID NO: 4 is "naturally occurring." However, that concern is more properly raised under a rejection under 35 U.S.C. § 112, second paragraph, rather than the written description requirement of the first paragraph.

The written description rejection is reversed.

2. Obviousness.

We initially note that appellants state that the claims are grouped together for the purposes of this rejection. Appeal Brief, page 5. Accordingly, we shall decide the issues raised in the Examiner's obviousness rejection as they pertain to claim 25. 37 CFR § 1.192(c)(7). We also note that the two Nishi references relied upon by the examiner appear to be the same. Thus, we shall consider the merits of the examiner's rejection as it is based upon Nishi '713.

Claim 25 is directed to a method for detecting a target polynucleotide said to comprise the polynucleotide of claim 7 in a sample. To this end, a sample is hybridized with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample. The probe will specifically hybridize to the target polynucleotide, if present, forming a hybridization complex. The presence or absence of the hybridization complex is an indication as to whether the sample contained the target polynucleotide.

The examiner has determined without dispute by appellants that Nishi '713 describes a polynucleotide encoding a carbohydrate metabolizing enzyme (glutamine:fructose-6-phosphate amidotransferase activity) that is 100% identical to the amino acid sequence set forth in SEQ ID NO:1 of this application. Examiner's Answer, page 6. The examiner has also determined, again without dispute by appellants, that Nishi '713 describes a polynucleotide sequence encoding that polypeptide that is 67.7% identical to the polynucleotide sequence set forth in SEQ ID NO:4 of this application. Id. The basis for the examiner's findings are the sequence comparison printouts

obtained as a result of an electronic search of sequence databases. As seen from the sequence search report dated December 14, 1999, U.S.-09-079-892-4.rng, pages 1-3 the polynucleotide sequence extending from nucleotide 99-2144 of SEQ ID NO:4 of this application is 100% identical to the coding sequence set forth in Nishi '713. See, e.g., Figs. 2A-2F and SEQ ID NO:5 of Nishi '713.

The examiner has concluded that it would have been obvious to a person of ordinary skill in the art to use any 20 contiguous nucleotides in the region of the polynucleotide sequence described in Nishi '713 as a probe in either a hybridization reaction or as part of a set of probes/primers in a PCR reaction to detect a target polynucleotide. Once again, appellants do not dispute this aspect of the examiner's position. Indeed, Nishi suggests as much, stating:

> The DNA encoding the protein or the partial peptide of the present invention can be cloned either by PCR amplification by using synthetic DNA primers having a partial nucleotide sequence of the DNA coding for the protein or by hybridization using the DNA inserted in a suitable vector and labeled DNA fragment or synthetic DNA coding for a part or full region of the protein or the partial peptide of the present invention. The hybridization can be carried out by the method described in Molecular Cloning, 2nd (J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989). When a commercially available DNA library is used, the instructions given in the accompanying manual can be followed.

Nishi '713, column 15, lines 54 through 65.

Where the appellants and the examiner part company in regard to the obviousness rejection has to do with whether claim 25 on appeal is "directed only to detecting the target polynucleotides, comprising the polynucleotides recited in claim [] 7 . . ." (Appeal Brief, page 12) or whether claim 25 is inclusive of "detecting any target polynucleotide which hybridizes to probes generated from the sequence of

Nishi. . .." (Appeal Brief, page 11) (emphasis in each original). Appellants urge that claim 25 must be read such that the claimed method detects only the polynucleotides recited in claim 7. We disagree with appellants' claim construction.

First, appellants' position does not take into account that claim 25 explicitly reads upon a negative result, i.e., the probe comprising at least 20 contiguous nucleotides will not hybridize to any nucleotide sequence in the sample. This is seen in that claim 25 b) includes detecting the absence of a hybridization complex. Since appellants have not contravened the basic premise of the examiner's obviousness rejection, i.e., it would have been obvious to one of ordinary skill in the art to use a probe comprising at least 20 contiguous nucleotides based upon the polynucleotide sequence described in Nishi '713 in a hybridization method, the performance of such a method that results in a negative result reads directly upon claim 25. Thus, the examiner's rejection can be sustained on this basis.

Second, we do not read claim 25 in the manner in which appellants do. In our view, claim 25 is not limited "only to detecting the target polynucleotides comprising the polynucleotides recited in claim [] 7 . . .." Appeal Brief, page 12. Once a probe comprising at least 20 contiguous nucleotides is constructed based upon the polynucleotide sequence described in Nishi '713, the use of that probe in a hybridization method will result in the hybridization complex being formed if the probe hybridizes to any polynucleotide sequence in the sample under the hybridization conditions used. Thus, an appropriately constructed probe based upon the polynucleotide sequence described in Nishi '713 will hybridize to a polynucleotide sequence such as that of Nishi

'713, that of SEQ ID NO:4 of this application or any other polynucleotide sequence having sufficient complementarity given the hybridization conditions used.

The examiner's obviousness rejection is affirmed.

The decision of the examiner is affirmed-in-part.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

Sherman D. Winters Administrative Patent Judge	)
William F. Smith Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Eric Grimes Administrative Patent Judge	)

Incyte Corporation
3160 Porter Drive
Palo Alto, CA 94304

dem

Paper No. 49

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JANICE A. KOLBERG
and MICHAEL S. URDEA

Appeal No. 1997-2532
Application No. 08/427,569[1]

ON BRIEF

Before WINTERS, SPIEGEL, and SCHEINER, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 17 through 36, which are all of the claims pending in this application.

The claimed invention is directed to sandwich hybridization assays for detecting HTLV-1 (claims 31-33), probes (claims 17-30) and kits (claims 34-36) therefore. Two

---

[1] Application for patent filed April 24, 1995. According to appellants, this application is a continuation of application 08/130,150 filed September 29, 1993, now abandoned, which is a continuation of application 07/813,585 filed December 23, 1991, now abandoned.

types of probes are claimed, i.e., amplifier and capture probes. Each probe has a first segment, i.e., an oligonucleotide of defined nucleic acid sequence, which hybridizes to a complementary distinct, separate nucleic acid sequence of the HTLV-1, thereby "sandwiching" the HTLV-1 between the probes. The capture probe (claims 20-22) has a second segment of nucleic acids complementary to the nucleic acid sequence of a solid phase oligonucleotide which allows separation of the complex of the sandwiched HTLV-1 from unreacted assay components, while the amplifier probe (claims 17-19) has a second segment of nucleic acids complementary to a "connecting" oligonucleotide segment of a "multimer." Neither second segment is complementary to an HTLV-1 nucleic acid sequence. In addition to the "connecting" oligonucleotide, the multimer also contains multiple oligonucleotides which are complementary to a labeled oligonucleotide. Thus, hybridization between the amplifier probe and the multimer ultimately "amplifies" the amount of label attached to the sandwich HTLV-1 via hybridization between the multimer and the labeled oligonucleotide. Claims 23-26 and 27-30 are directed to sets of two or more amplifier probes having different first segments and sets of two or more capture probes having different first segments. The first segments of the amplifier and capture probes comprise sequences selected from SEQ ID NOs. 6-41 and SEQ ID NOs. 42-53, respectively.

Claims 23 and 31 are illustrative and read as follows:

23. A set of synthetic oligonucleotides useful as amplifier probes in a sandwich hybridization assay for HTLV-1, comprising at least two different oligonucleotide probes, wherein each oligonucleotide probe consists of:

a first segment having a minimum length of about 25 nucleotides and a maximum length of about 100 nucleotides which segment is at least 90% homologous to a segment of HTLV-1 nucleic acid, wherein said first segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS: 6-41; and

a second segment consisting of a nucleotide sequence which is at least 90% homologous to an oligonucleotide segment of a nucleic acid multimer wherein said second segment is not complementary to HTLV-1 nucleic acid;

and optionally one or more noncomplementary segments each consisting of a nucleotide sequence that is not complementary to HTLV-1 nucleic acid.

31. A solution sandwich hybridization assay for detecting the presence of HTLV-1 in a sample, comprising:

(a) contacting the sample with (i) amplifier probes comprising the set of synthetic oligonucleotides of claim 23 and (ii) a set of capture probe oligonucleotides wherein there is a molar excess of amplifier probes and of capture probes over analyte nucleic acid in the sample, wherein said set of capture probe oligonucleotides comprises at least two different oligonucleotides each of which consists of

a first segment having a minimum length of about 25 nucleotides and a maximum length of about 100 nucleotides which segment is at least 90% homologous to a segment of HTLV-1 nucleic acid, wherein said first segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS: 42-53; and

a second segment consisting of a nucleotide sequence which is at least 90% homologous to an oligonucleotide bound to a solid phase wherein said second segment is not complementary to HTLV-1 nucleic acid;

and optionally one or more noncomplementary segments each consisting of a nucleotide sequence that is not complementary to HTLV-1 nucleic acid;

(b) contacting the product of step (a) with said oligonucleotide bound to the solid phase;

(c) thereafter separating materials not bound to the solid phase;

(d) contacting the bound product of step (c) with a nucleic acid multimer, said multimer comprising at least one oligonucleotide segment that is at least 90% homologous to the second segment of the amplifier probe polynucleotide [sic, oligonucleotide] and a multiplicity of second oligonucleotide segments that are at least 90% homologous to a labeled oligonucleotide;

(e) removing unbound multimer;

(f) contacting the solid phase complex product of step (e) with the labeled oligonucleotide;

(g) removing unbound labeled oligonucleotide; and

(h) detecting the presence of label in the solid phase complex product of step (g) and, thereby, detecting the presence of virus in the sample.

The references relied on by the examiner are:

Hogan et al. (Hogan) (published International Application)	WO 88/03957	June 2, 1988
Urdea et al. (Urdea) (published International Application)	WO 89/03891	May 5, 1989

Seiki et al. (Seiki), "Human adult T-cell leukemia virus: Complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA," Proceedings of the National Academy of Sciences, USA, Vol. 80, pp. 3618-3622 (June 1983).

Stratagene 1988 Catalog, p. 39 (Stratagene).

Ratner et al. (Ratner), "Nucleotide Sequence Analysis of Isolates of Human T-Lymphotropic Virus Type I of Diverse Geographical Origins," AIDS Research and Human Retroviruses, Vol. 7, No. 11, pp. 923-941 (November 1991).

ISSUES[2]

[2] The examiner withdrew the final rejection of claims 17-36 under 35 U.S.C. § 112, first paragraph, as lacking enablement (see answer, para. bridging pp. 7-8).

Claims 17-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner. Claims 34-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner and further in view of Stratagene. We REVERSE both rejections.

In reaching our decision in this appeal we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's answer (Paper No. 42, mailed November 26, 1996) for the examiner's reasoning in support of the rejection and to the appellants' brief (Paper No. 41, filed September 26, 1996) and to appellants' reply brief (Paper No. 43, filed January 24, 1997)[3] for the appellants' arguments thereagainst.

OPINION

Urdea discloses a generic solution sandwich hybridization assay comprising (a) contacting a sample with (i) an amplifier probe having a first segment that is complementary to a first portion of a nucleic acid sequence of interest and a second segment that is complementary to a oligonucleotide unit of a nucleic acid multimer and (ii) a capture probe having a first segment that is complementary to a second, different portion

[3] After initially denying entry of appellants' reply brief in a communication mailed February 25, 1997 (Paper No. 44), the examiner later entered the reply brief "[i]n view of the new rules for entry of reply briefs which went into effect December 1, 1997, which require the entry of reply briefs" (see communication mailed December 12, 1997, Paper No. 47).

of the nucleic acid sequence of interest and a second segment that is complementary to an oligonucleotide bound to a solid phase; (b) contacting the product of step (a) with the oligonucleotide bound to the solid phase; (c) thereafter separating materials not bound to the solid phase; (d) contacting the product of step (c) with the nucleic acid multimer, wherein the multimer comprises at least one oligonucleotide that is complementary to the second segment of the amplifier probe and a multiplicity of second oligonucleotide units that are complementary to a labeled oligonucleotide;
(e) removing unbound multimer; (f) contacting the product of step (e) with the labeled oligonucleotide; (g) removing unbound labeled oligonucleotide; and (h) detecting the presence of label in the product of step (g) to detect the presence of the nucleic acid sequence of interest in the sample (see e.g., claim 12; pp. 3, 7, 24-27 and 31-32; Example 3, pp. 46-49). While Urdea exemplifies assays, reagents and kits for detecting hepatitis B virus, Neisseria gonorrhoeae and Chlamydia trachomatis, "Urdea does not teach the use of any HTLV-1 sequences nor a methodology for selecting any specific HTLV-1 sequences" (answer, p. 4, last sentence). In other words, Urdea does not disclose or suggest amplifier and capture probes having first segments selected from the group consisting of SEQ ID NOs. 6-41 and SEQ ID NOs. 42-53, respectively.

Seiki "reports the complete 9,032-nucleotide sequence of the proviral genome [of HTLV-1] cloned in •ATK-1" (p. 3618, sentence bridging cc. 1-2; Fig. 2) and points "out that

the predicted viral genome ... could be tentative, because the provirus analyzed ... is that integrated in leukemia cells" (p. 3622, c. 2, first full para.).

Hogan discloses a method for preparing probes for use in hybridization assays which

> comprises constructing an oligonucleotide that is sufficiently complementary to hybridize to a region of rRNA selected to be unique to a non-viral organism or group of non-viral organisms sought to be detected, said region of rRNA being selected by comparing one or more variable region rRNA sequences of said non-viral organism or group of non-viral organisms with one or more variable region rRNA sequences from one or more non-viral organisms sought to be distinguished" (abstract).

Ratner determined the sequences for nucleotides 1-5184, including the long terminal repeat (LTR), *gag*, protease gene, and *pol* sequences, of HTLV-1 isolates of Caribbean and African origin (abstract; p. 924, c. 1, para 3; Fig. 1) and stated that

> [t]he limited sequence variation among HTLV-1 isolates suggests that diagnostic assays should be useful in detecting virtually all substrains of the virus. The positions of sequence variation outlined here should assist in the design of future diagnostic reagents. [P. 939, c. 2, para. 2.]

Stratagene describes two advantages of kits, convenience and quality control.

According to the examiner, it would have been obvious (a) to identify conserved regions of the HTLV-1 sequence disclosed by Seiki or Ratner (b) using the "the methodology of selection of particular primers as taught by Ratner or Hogan" (c) "to solve the problem of specific detection of a variety of HTLV-1 species" using the hybridization assay of Urdea (d) "since Ratner states 'The limited sequence variation among HTLV-1

isolates suggests that diagnostic assays should be useful in detection [sic, detecting] virtually all substrains of the virus. The positions of sequence variation outlined here should assist in the design of future diagnostic reagents.' " (answer, p. 6). Thus, the dispositive issue is whether the "methodology of selection" of Ratner or Hogan (or any other applied prior art reference) discloses or suggests the claimed synthetic oligonucleotides comprising a first segment selected from SEQ ID NOs. 6-41 and from SEQ ID NOs. 42-53 suitable for use as amplifier and capture probes, respectively, in a solution sandwich hybridization assay for HTLV-1.

First, we note that neither appellants nor the examiner appear to appreciate that Hogan is directed to nucleic acid probes for non-viral organisms based on unique rRNA sequences (see e.g., p. 3, ll. 22-30) found in 5S rRNA, 16S rRNA and 23S rRNA (see e.g., p. 9; claim 5). Hogan expressly states, "With the exception of viruses, all prokaryotic organisms contain rRNA molecules including 5S rRNA, 16S rRNA, and a larger rRNA molecule known as 23S rRNA" (emphasis added, p. 9, ll. 5-8). There is no evidence of record establishing that HTLV-1 contains 5S rRNA, 16S rRNA and/or 23S rRNA. The examiner has not provided any fact-based or reasoned explanation of why one of ordinary skill in the art would have looked to Hogan's method of selecting non-viral probes for detecting non-viral organisms for guidance in selecting viral nucleic acid probes for

detecting a virus with any reasonable expectation of success of obtaining oligonucleotides comprising SEQ ID NOs. 6-53 as specifically claimed.

Second, the examiner has failed to point out, and we do not find, where Ratner provides any particular recognition or suggestion of the specific sequences, i.e., SEQ ID NOs. 6-53, required by the claimed invention.

None of Urdea, Seiki or Stratagene provide any particular recognition or suggestion of SEQ ID NOs 6-53 as required by the claimed invention. Therefore, in our view the examiner's rejection can be aptly characterized as an "obvious to try" rejection, i.e., obvious to try any nucleotide sequence contained within the 9,000-plus nucleic acid HTLV-1 genome. Simply opining that "any oligonucleotide probe from the HTLV-1 sequences of Ratner or Seiki are deemed functionally equivalent to the claimed oligonucleotides" (answer, p. 12), without a factual basis supporting that opinion, is insufficient to establish a conclusion of obviousness. As stated in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)

> ... what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (citations omitted).

Accordingly, we find the examiner has not carried his burden of establishing a prima facie case of obviousness. Having concluded that the examiner has not established a prima facie case of obviousness, we do not reach the rebuttal declaratory evidence discussed in appellants' brief (pp. 9, 16, 19-22 and 30-32) and reply brief (pp. 8 and 11).

The rejections of claims 17-36 under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner alone or further in view of Stratagene are reversed.

OTHER MATTERS

The transitional phrases "comprising," "consisting essentially of" and "consisting of" are terms of art which define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. "Comprising" is open-ended and does not exclude additional, unrecited components or method steps, while "consisting of" is close-ended and excludes any component or step not specified in the claim. "Consisting essentially of" occupies a middle ground and limits the scope of a claim to the specified components or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. See e.g., the MPEP, 7th ed. (rev. 1, February 2000), at § 2111.03.

Here, the claims appear to use these terms in a non-traditional manner which gives rise to internal inconsistencies. For example, claim 17 recites an oligonucleotide which consists of a first segment which comprises, i.e., is open to the inclusion of, nucleotides over and beyond those of a specified a selected sequence, a second segment which consists of a sequence at least 90% homologous to another sequence, and optionally one or more noncomplementary sequences. Thus, the closed scope of the oligonucleotide of claim 17 is open to the inclusion of additional, unrecited nucleic acids and optional sequences.

As represented to us by appellants, this non-traditional term usage appears to have arisen at the suggestion of the examiner.[4] However, in view of the apparent inconsistencies arising from this non-traditional term usage, appellants and the examiner should review any allowable claims prior to issuance in light of the art-recognized definition

---

[4] According to appellants,

> The first and second segments [of the claimed probes and probe sets] as defined constitute the only essential structural features of the optimized HTLV-1 probes. However, since a user can included additional "filler" sequence that is not complementary to HTLV-1 (and is therefore unlikely to impact hybridization) as described in the specification, the claims were originally written with the open claim language "comprising". In consultation with the Examiner of the predecessor application, it was considered preferable to employ the closed claim language "consisting of" and to specifically recite the noncomplementary sequence as an optional element. Applicants previously adopted the former Examiner's suggestions in an effort to expedite prosecution, and that language is reflected in the pending claims. [Emphasis added, brief, fn. 1.]

of "comprising," "consisting essentially of" and "consisting of" to ensure that claims of proper scope issue.

CONCLUSION

In conclusion, the decision of the examiner (1) to reject claims 17-33 under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner is reversed, and (2) to reject claims 34-36 under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner and further in view of Stratagene is reversed.

REVERSED

SHERMAN D. WINTERS)
Administrative Patent Judge)

	)
	)
	)
	) BOARD OF PATENT
CAROL A. SPIEGEL	) APPEALS
Administrative Patent Judge	) AND
	) INTERFERENCES
	)
	)
	)
TONI R. SCHEINER	)
Administrative Patent Judge	)

Appeal No. 1997-2532
Application No. 08/427,569

CS/dm

KENNETH M. GOLDMAN
CHIRON CORPORATION
INTELLECTUAL PROPERTY R440
P.O. BOX 8097
EMERYVILLE, CA 94662-8097

APPEAL NO. 1997-2532 - JUDGE SPIEGEL
APPLICATION NO. 08/427,569

APJ SPIEGEL

APJ WINTERS

APJ SCHEINER

DECISION: **REVERSED**

Prepared By:

DRAFT TYPED: 02 Jul 01

FINAL TYPED:

Paper No. 44

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RALPH R. WEICHSELBAUM, DENNIS E. HALLAHAN, VIKAS P. SUKHATME, and DONALD W. KUFE

Appeal No. 1999-1458
Application No. 07/943,812

ON BRIEF[1]

Before WINTERS, WILLIAM F. SMITH, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 3-21, 36, 38-41, 48-50 and 52-59, which are all the claims pending in the application.

---

[1] Pursuant to appellants request (Paper No. 39, received September 18, 1998) an oral hearing for this appeal was scheduled for Tuesday, October 9, 2001. Appellants, however, waived (Paper No. 43, received October 2, 2001) their request for oral hearing. Accordingly, we considered this appeal on Brief.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. An isolated and purified DNA molecule comprising a radiation responsive enhancer-promoter operatively linked to an encoding region that encodes at least one polypeptide, other than CAT, that one desires to have expressed in a radiation responsive manner, which encoding region is operatively linked to a transcription-terminating region, wherein said radiation responsive enhancer-promoter comprises a portion of the CArG domain from –550 to –50 of an Egr-1 promoter or a c-jun promoter.

The references relied upon by the examiner are:

Hung et al. (Hung)	4,370,417	Jan. 25, 1983
Mark et al. (Mark)	4,677,064	Jun. 30, 1987
Brent et al. (Brent)	4,833,080	May 23, 1989
Orr et al. (Orr)	4,835,098	May 30, 1989

Johnsson et al. (Johnsson), "The c-sis Gene Encodes a Precursor of the B Chain of Platelet-Derived Growth Factor," The EMBO Journal, Vol. 3, No. 5, pp. 921-928 (1984)

Angel et al. (Angel), "The Jun Proto-Oncogene is Positively Autoregulated by Its Product, Jun/AP-1," Cell, Vol. 55, pp.875-885 (1988)

Bonthron et al. (Bonthron), "Platelet-Derived Growth Factor A Chain: Gene Structure, Chromosomal Location, and Basis for Alternative mRNA Splicing," Proc. Natl. Acad, Vol. 85, pp. 1492-1496 (1988)

Christy et al. (Christy), "A Gene Activated in Mouse 3T3 Cells by Serum Growth Factors Encodes a Protein With 'Zinc Finger' sequences," Proc. Natl. Acad, Vol. 85, pp. 7857-7861 (1988)

Ghosh et al. (Ghosh), "Cloning of the p50 DNA Binding Subunit of NF- κB: Homology to rel and dorsal," Cell, Vol. 62, pp. 1019-1029 (1990)

Moolten et al. (Moolten), "Curability of Tumors Bearing Herpes Thymidine Kinase Genes Transferred by Retroviral Vectors," Journal of the National Cancer Institute, Vol. 82, No. 4, pp. 297-300 (1990)

GROUNDS OF REJECTION

Claims 1, 3-21, 36, 48 and 52-55 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of nucleotide numbers because the frame of reference is not clearly defined.

Claims 1, 3-21, 36, 38-41, 48-50 and 52-59 stand rejected under 35 U.S.C. § 103 as being unpatentable over Christy or Angel in view of any one of Bonthron, Johnsson, Mark, Moolten, Hung, Orr, Ghosh or Brent.

We reverse and raise other issues for the examiner's consideration.

DISCUSSION

In reaching our decision in this appeal, we considered appellants' specification and claims, in addition to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer[2] for the examiner's reasoning in support of the rejections. We further reference appellants' Brief[3], and appellants' Reply Brief[4] for the appellants' arguments in favor of patentability. We note the examiner entered and considered the Reply Brief.[5]

[2] Paper No. 38, mailed July 14, 1998.
[3] Paper No. 37, received May 11, 1998.
[4] Paper No. 39, received September 18, 1998.
[5] Paper No. 40, mailed October 1, 1998.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

As set forth in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991):

> The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits.").

Furthermore, claim language must be analyzed "not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

According to the examiner (Answer, page 4) "[c]laims 1, 54 and 55 are indefinite in their recitation of nucleotide numbers because the frame of reference (i.e. which base is "0" or "1") is not clearly defined." In response, appellants argue (Brief, page 5) that:

> [A]s a matter of scientific convenience, the base numbering of upstream regulatory regions typically relates to the start of transcription for the corresponding gene. Thus, even if there were no information in the literature on the numbering for these particular genes, and no guidance in the instant specification as to what regions are encompassed by the recitation of "-550 to –50," the claims would, nonetheless, be clear. Those of skill in the art would understand the claims to include those residues that are 50 to 550 bases upstream of the translational start site, simply by convention.

With reference to page 14, "Scheme 1" of the specification, appellants argue (Brief, page 6) that this "convention is used in the instant specification." However, the examiner argues (Answer, page 7) that while "[a]ppellants argue that one skilled in the art would know that nucleotide '0' is the transcriptional start site ... the convention is that the transcriptional start site is nucleotide '1,' not '0'." In response, appellants argue (Reply Brief, page 4) "the 'conventional' numbering to which the examiner refers, where '+1' is the start, also used [sic] '-1' as one base before the start. Thus, '-550 to –50' is the same for both." We agree with appellants. We also note that in "SCHEME 1" of the specification (page 14) "+1" is defined as "0".

The examiner also finds (Answer, page 7) that "Angel et al. indicate that the jun gene has at least three transcriptional start sites. They state, '[t]he major start site of transcription was arbitrarily numbered +1' (Fig. 4) and later refer to 'two minor start sites' (p. 878, col. 1)." In response, appellants argue (Reply Brief, page 4), "Scheme 1 indicates the general position of the defined start site, if for no other reason, than the spacing of the six CArG domains." As we noted above, "SCHEME 1" of the specification (page 14) defines "+1" as "0." Therefore, regardless of the existence "minor start sites," Angel defined the "+1" site, this site to appellants specification is defined as "0" and is therefore the "frame of reference" from which –550 to –50 are determined.

Therefore, in our opinion, the claims reasonably apprise those skilled in the art as to their scope. Accordingly, we reverse the rejection of claims 1, 3-21, 36, 48 and 52-55 under 35 U.S.C. § 112, second paragraph.

THE REJECTION UNDER 35 U.S.C. § 103:

The examiner finds (Answer, bridging sentence, page 4) that Christy "disclose[s] DNA constructs comprising the Egr-1 ... promoter linked to the CAT reporter gene... [demonstrating] that a heterologous gene can be expressed under control of the Egr-1 promoter...." In addition, the examiner finds (Answer, page 5) that Angel "demonstrate[s] that a heterologous gene can be expressed under control of the c-jun promoter...." However, the examiner finds (id.) that "[n]either Christy et al. nor Angel et al. disclose DNA constructs in which the promoter is linked to a gene encoding a 'therapeutic' polypeptide."

To make up for the deficiency of Christy and Angel, the examiner relies (Answer, page 5) on any one of Bonthron, Johnsson, Mark, Moolten, Hung, Orr, Ghosh or Brent, which teach the coding sequence of various proteins. With this the examiner concludes (Answer, page 6) that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to link either of the promoters taught by Christy et al. and Angel et al. to any of the coding sequences disclosed by Bonthron et al., Johnsson et al., Mark et al., Moolten et al., Hung et al., Orr et al., Ghosh et al. or Brent et al., in order to express the coding sequence.

According to the examiner (Answer, page 8) a person "of ordinary skill in the art knew that any coding sequence could be linked to any promoter for expression of the coding sequence. It is obvious to substitute known equivalents for the same purpose, even if there is not an express suggestion to substitute one equivalent component for another...." On the surface, the examiner appears to make out a reasonable prima facie case of obviousness. We note that when the prior art recognizes two components to be equivalent, an express suggestion to

substitute one for another need not be present in order to render such substitution obvious. In re Fout, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982).

According to appellants (Brief, page 9), the examiner ignored their unexpected results. Specifically, appellants argue (Brief, pages 9-10) that "[t]here is no teaching or suggestion in the prior art regarding the radiation inducibility of the claimed constructs ... [t]he examiner has not disputed these facts and even admits that the radiation inducibility of the claimed constructs was nonobvious." To this the examiner argues (Answer, page 9), "[t]here is no evidence of unexpected results. Radiation inducibility is a previously unknown property of the jun and Egr-1 promoters, not an unexpected result of combining the promoters with any coding sequence other than CAT." Once again, on the surface, there is some merit to the examiner's argument. As set forth in In re Dillon, 919 F.2d 688, 693, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc):

> There is no question that all evidence of the properties of the claimed compositions and the prior art must be considered in determining the ultimate question of patentability, but it is also clear that the discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a prima facie case. ... [In re Shetty, 566 F.2d 81, 86, 195 USPQ 753, 756 (CCPA 1977)]. Each situation must be considered on its own facts, but it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant.

In In re Shetty, 566 F.2d 81, 86, 195 USPQ 753, 756 (CCPA 1977), the court found that:

> Appellant merely shows that his novel compounds are appetite suppressants whereas the reference compounds are not so known. ... Presented with such an absence of comparative or other evidence with respect to the properties of the compounds and the claimed composition, we hold that [the] composition ... would have been obvious from and unpatentable over the prior art.

These cases appear to be consistent with the examiner's conclusion (Answer, page 11) that "[a]ppellants discovered that the promoters are ... induced by radiation. On the basis of this discovery, they wish to exclude others from using the promoters in combination with any coding sequence other than CAT, for any purpose. The [e]xaminer's interpretation of the law is that this is not permitted." But, if one looks under the surface, the facts of record in this case do not lead to the examiner's conclusion.

The claimed invention is drawn to "[a]n isolated and purified DNA molecule comprising a radiation responsive enhancer-promoter operatively linked to an encoding region that encodes at least one peptide, other than CAT...." According to the examiner (Answer, page 9), that the claimed promoter is radiation responsive is an inherent property of the promoter; it is not the "unexpected" result of combining this regulatory sequence (promoter) with a structural sequence other than CAT. We agree with this part of the examiner's analysis. However, the analysis does not end there.

In responding to appellants' arguments it appears that the examiner more fully develops his prima facie case of obviousness. According to the examiner (Answer, pages 8-9) "[t]hose of ordinary skill in the art knew that any coding sequence could be linked to any promoter for expression of the coding sequence. It is obvious to substitute known equivalents for the same purpose,

even if there is not an express suggestion to substitute one equivalent component for another." It is this statement, however, that illustrates the deficiency in the examiner's prima facie case. As we understand the examiner's reasoning, as a general proposition, it would have been obvious to substitute known equivalent coding sequences, or known equivalent promoters.

It is, however, not entirely clear on this record what the examiner may mean by equivalent coding sequences. Furthermore, we find that the examiner has not established that the coding sequences are "equivalent." Instead, the examiner finds (Answer, page 5) that each coding sequence encodes a different protein. Without a showing of equivalence the examiner has not established a prima facie case of obviousness.

That leaves the promoters. The examiner's position appears to be, since the promoters of either Angel or Christy are "equivalent" to the promoters set forth in the secondary references it would be obvious to substitute one for the other. The examiner, however, failed to demonstrate that any of the promoters used by the secondary references are in fact radiation responsive, and therefore "equivalent" to the promoter of either Angel or Christy. Stated differently, there is no evidence on this record demonstrating that the promoters of the secondary references are radiation responsive. Therefore, there is no evidence on this record that the Angel or Christy promoters are equivalent to the promoters of the secondary references. Without a showing of equivalence the examiner has not established a prima facie case of obviousness.

In contrast to the facts in evidence on this record, in Dillon, 919 F.2d at 692, 16 USPQ2d at 1900-01 there was an art recognized equivalence between the tri-orthoesthers of the primary reference and the tetra-orthoesthers of the secondary reference. In Shetty, cited in Dillon, the structural similarity between the prior art compound and the claimed compound was such that one would have expected the two compounds to possess similar properties; evidence of unexpected properties was not of record. On this record, there is no evidence that the prior art structural genes are equivalent to each other. Furthermore, there is no evidence that appellants' promoter is equivalent to the prior art promoters. In addition, appellants demonstrate that their promoter has an unexpected advantage over other promoters (such as those found in the secondary references); specifically appellants' promoter is radiation responsive.

On reflection, in our opinion, there is no suggestion for combining the teachings of the references relied upon by the examiner in a manner that would have reasonably led one of ordinary skill in this art to arrive at the claimed invention. The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). On this record, the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. Accordingly, we reverse the rejection of claims 1, 3-21, 36, 48-50 and 52-59 under 35 U.S.C. § 103 as being unpatentable over Christy or Angel in view of any one of Bonthron, Johnsson, Mark, Moolten, Hung, Orr, Ghosh or Brent.

OTHER ISSUES:

We offer the following observations for the examiner's consideration.

I. Tsai-Morris:

Upon review of this administrative file, we note that Tsai-Morris[6] appears to correspond to at least claim 1 of appellants' claimed invention. Specifically, Tsai-Morris teach "the isolation of a mouse Egr-1 genomic clone, its intron-exon structure and 935 bp of 5' flanking sequence. The gene spans about 3.8 kb and consists of 2 exons and one 700 bp intron." See abstract. In addition, Tsai-Morris teach (id.) that this clone contains "five elements whose sequence is nearly identical to the inner core 10 nucleotide region (CCATATTAGG) of the c-Fos serum response element...." We note that appellants specification defines the claimed CArG domain as a "serum response or $CC(A/T)_6GG$" domain. In addition, we note that this DNA molecule is expected to encode at Egr-1, which is a polypeptide other than CAT.

Upon return of this application, the examiner should take a step back and determine whether Tsai-Morris anticipates the claimed invention. In this regard, we note as set forth in In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990):

> discovery of an unobvious property and use does not overcome the statutory restraint of section 102 when the claimed composition is known. While Spada's position is that his polymers are not anticipated by the polymers of Smith because their properties are different, Spada was reasonably required to show that his polymer compositions are different from those described by Smith. This burden was not met by simply including the assertedly different properties in the claims. When the claimed compositions are not

[6]Tsai-Morris et al. (Tsai-Morris), "5' flanking sequence and genomic structure of Egr-1, a murine mitogen inducible zinc finger encoding gene," Nucleic Acids Research, Vol. 16, No. 18, pp. 8835-8846 (1988).

> novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.

II. Written Description:

As set forth in UC v. Eli Lilly and Co., 119 F. 3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Furthermore, Lilly 119 F.3d at 1568, 43 USPQ2d at 1406, indicates, "[a] definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." In this regard, we note, for example, that unlike appellants' claim 1, wherein the radiation responsive enhancer-promoter comprises a portion of the Egr-1 or c-jun promoter, claims 56-59 are broadly drawn to any "isolated and purified DNA molecule comprising a radiation responsive enhancer promoter."

Upon return of this application, the examiner should take a step back and determine whether appellants' specification provides an adequate written description of any "isolated and purified DNA molecule comprising a radiation responsive enhancer promoter" as set forth in claims 56-59.

REVERSED

Sherman D. Winters)
Administrative Patent Judge)
)

	)
	) BOARD OF PATENT
William F. Smith	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
Donald E. Adams	)
Administrative Patent Judge	)

DA/dym

Ronald B. Cooley
Arnold, White & Durkee
P.O. Box 4433
Houston, TX 77210